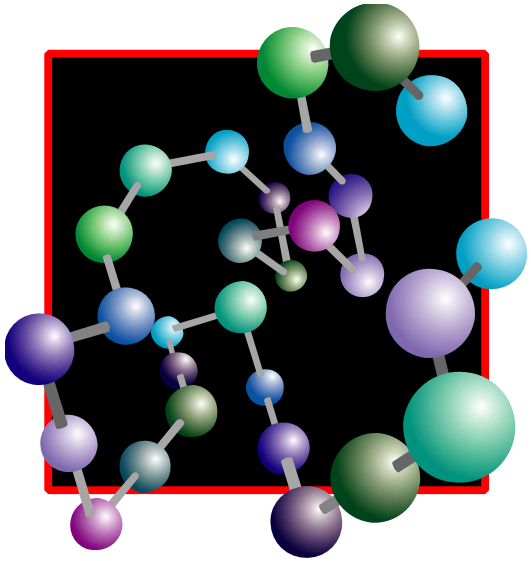
Polymer-Populations Mapping

Evolutionary Cell Biology 2015
KITP Santa Barbara

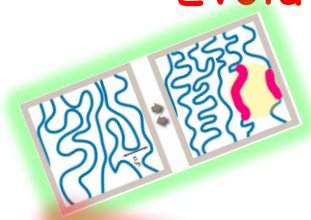
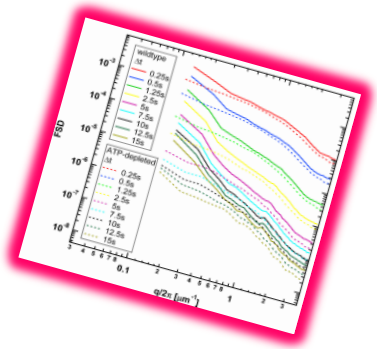
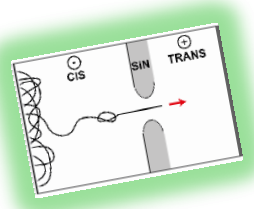
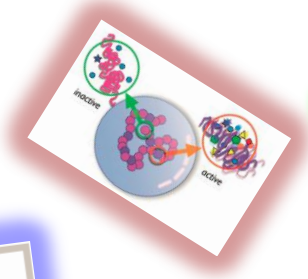
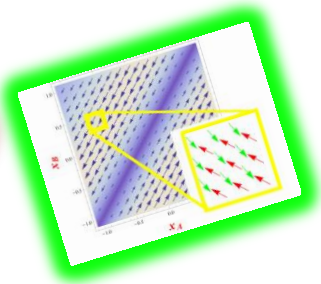


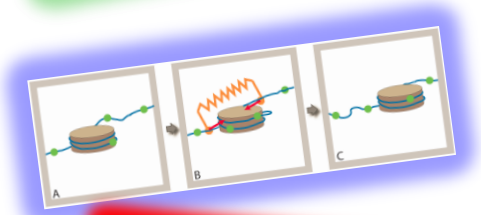
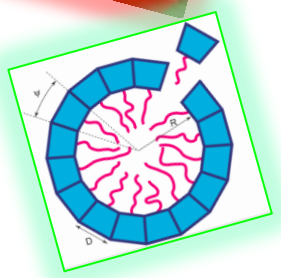
Alexander Grosberg, New York University, Physics Department and
Center for Soft Matter Research

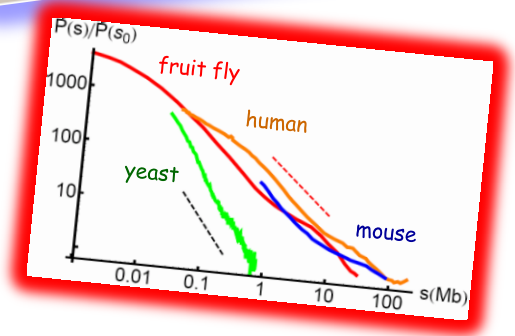
E.Kussel (NYU), Y.Wakamoto (Tokyo), S.Leibler (Rockefeller)

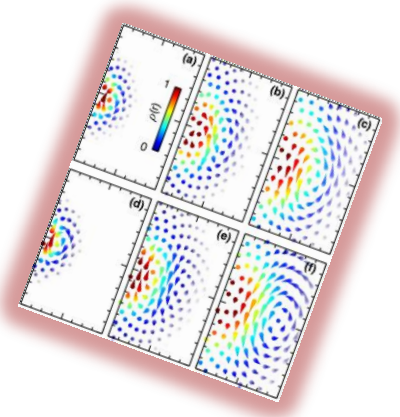
My recent topics:

- Nuclear physics: (1) Territories, (2) Nuclear chromodynamics.
- Activity and dissipation driven phase separation.
- Topology of polymer rings, branched polymers.
- RNA viruses, self-assembly.
- Electrophoresis and knots detection in DNA.
- Brownian vertex, a novel type of stochastic engine.
- Evolution appears to have suppressed proteins with knots; why?





- Polymer-Population Mapping and Localization in the Space of Phenotypes, with E.Kussel and S.Leibler (Phys. Rev. Let., v. 97, 068101, 2006)*.
- Optimal Lineage Principle for Age-Structured Populations, with Y.Wakamoto and E.Kussell (Evolution, v. 66, p. 115–134, 2012).

*Excluding self-citations, cited only 3 times

Sensing or guessing?

Phenotypic Diversity, Population Growth, and Information in Fluctuating Environments

Edo Kussell* and Stanislas Leibler

Organisms in fluctuating environments must constantly adapt their behavior to survive. In clonal populations, this may be achieved through sensing followed by response or through the generation of diversity by stochastic phenotype switching. Here we show that stochastic switching can be favored over sensing when the environment changes infrequently. The optimal switching rates then mimic the statistics of environmental changes. We derive a relation between the long-term growth rate of the organism and the information available about its fluctuating environment.

Organisms adapt readily to regularly varying environments, for instance, by adjusting to the daily light cycles by using internal circadian clocks. Real problems arise when environmental fluctuations are irregular. Organisms can adapt to sudden changes in chemical composition, local temperature, or illumination by sensing the changes and responding appropriately, for example, by switching phenotype or behavior. But there is a cost: each individual must maintain active sensory machinery.

Population diversity offers an alternate way to adapt to randomly fluctuating environments. Different subsets of the total population may be well-adapted to different types of environments. In genetically clonal populations, phenotypic diversity is generated by stochastic phenotype-switching mechanisms (*1 9*). Examples include flagellin phase variation in *Salmonella enterica* (*6*); microsatellite length variation (slipped-strand mispairing), controlling the expression of contingency genes in *Haemophilus influenzae* (*2*, *4*); and swarming motility in *Bacillus subtilis* (*8*). The persistence mechanism in *Escherichia coli*, by which cells switch spontaneously and reversibly to a phenotype exhibiting slower growth and reduced killing by antibiotics (*9*), allows cells to survive prolonged exposure to antibiotics (*10*). Many other switching mechanisms are known in diverse bacteria (*2*, *7*), fungi (*1 3*), and slime molds (*1*).

The idea that randomization of phenotype can be advantageous in fluctuating environments is well established in the ecology and population genetics literature (where it is known as bet-hedging). This idea has found applications in diverse contexts (*11*), and it was previously analyzed in several theoretical and computational studies (*12 18*).

We consider two extreme types of phenotype switching: responsive switching (*R*), occurring as a direct response to an outside cue detected by a sensing mechanism, and spontaneous stochastic switching (*S*), occurring without any direct sensing of the environment. Within a theoretical model, we address several questions. First, under which circumstances should each mechanism be used? For instance, if the detection of a sudden unfavorable environmental change, or the subsequent response, would be too slow, then it could be advantageous to have a subpopulation ready in an appropriate phenotype, before the environmental change.

Second, what determines parameters such as the switching rates? Random environmental

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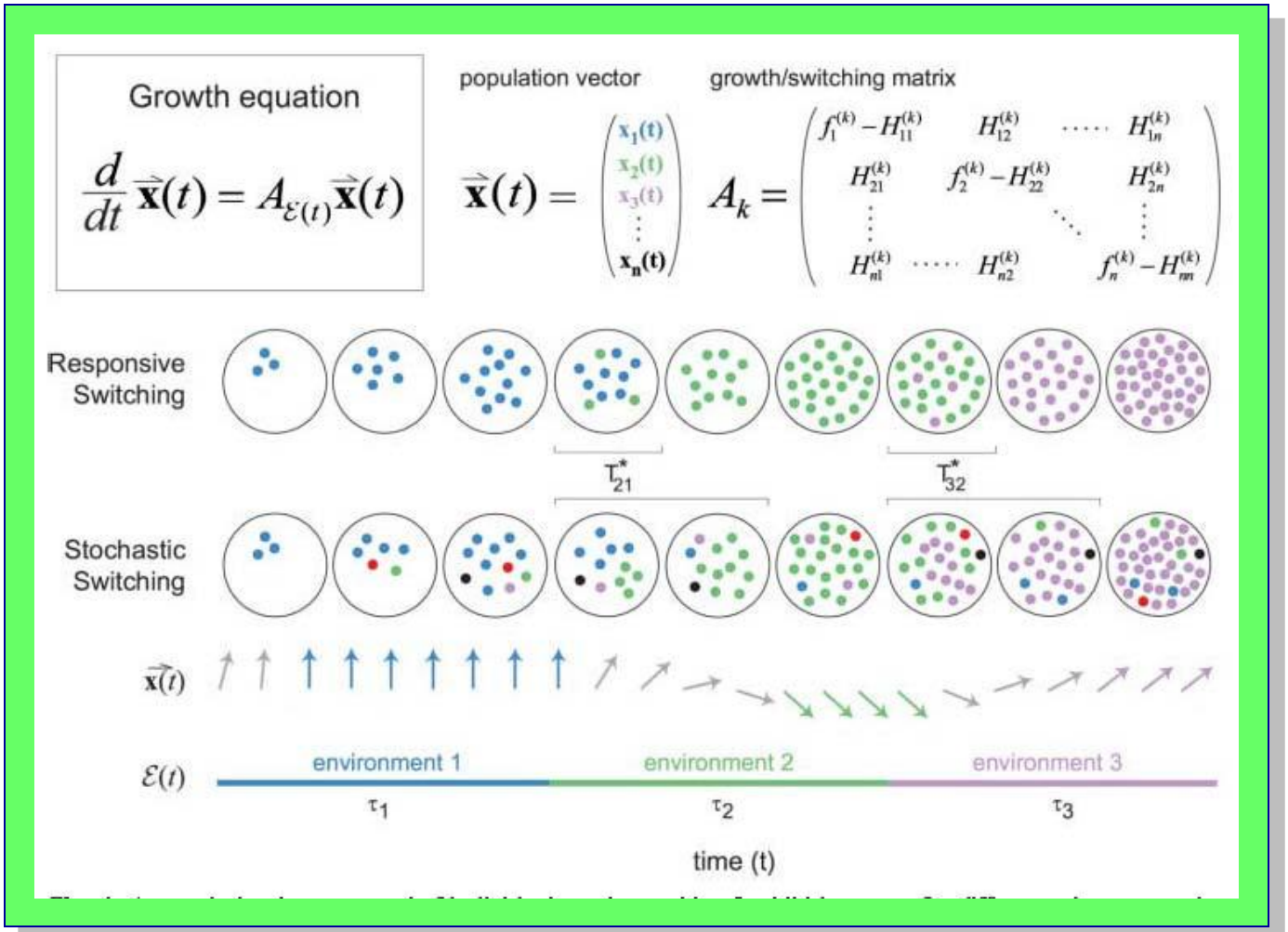
Population vector dynamics



Product of non-commuting matrices

"The same equations have the same solutions"
Feynman Lectures in Physics, v. 2, lecture 12 on "Electrostatic Analogies"

- Populations:

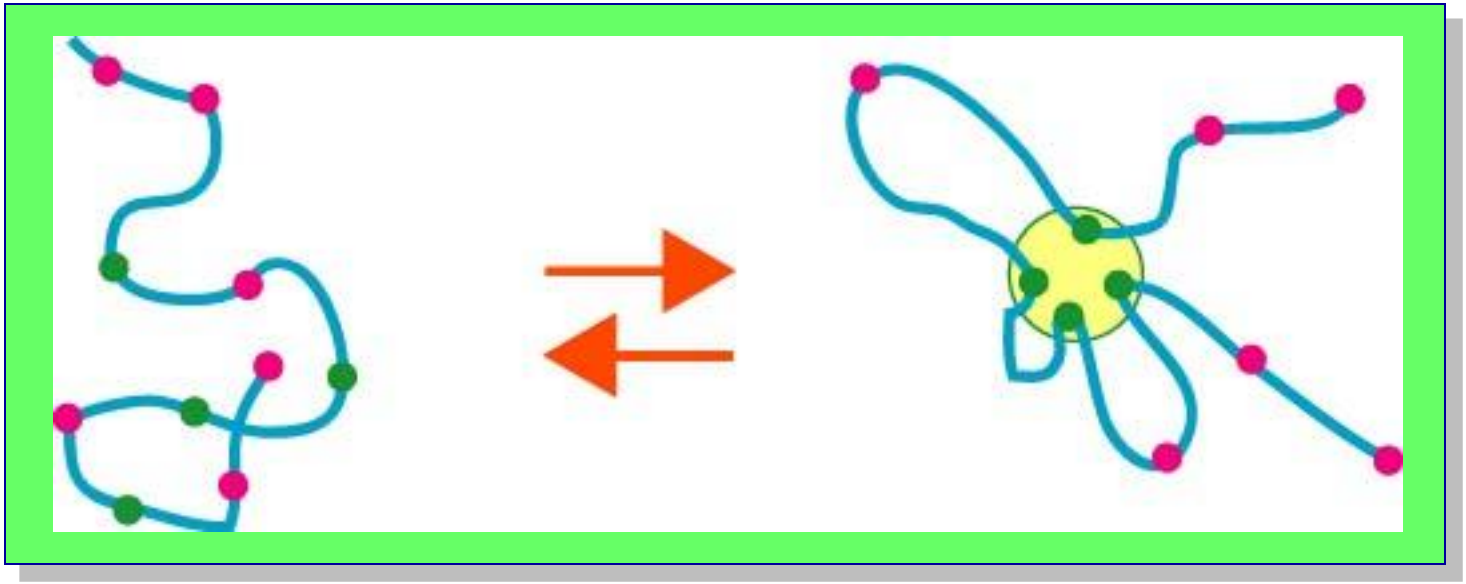
$$\frac{d}{dt}X_i(t) = f_i^{\mathcal{E}}X_i(t) + \sum_j h_{ij}X_j(t).$$

- Heteropolymers:

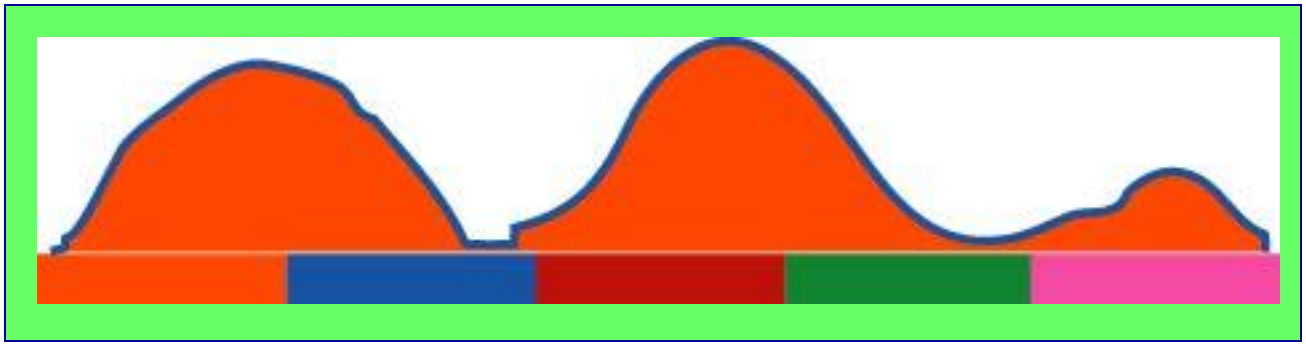
$$\frac{d}{dt}G_r(t) = -\frac{\phi_r^{\alpha}}{T}G_r(t) + a^2\nabla^2 G_r(t).$$

Examples:

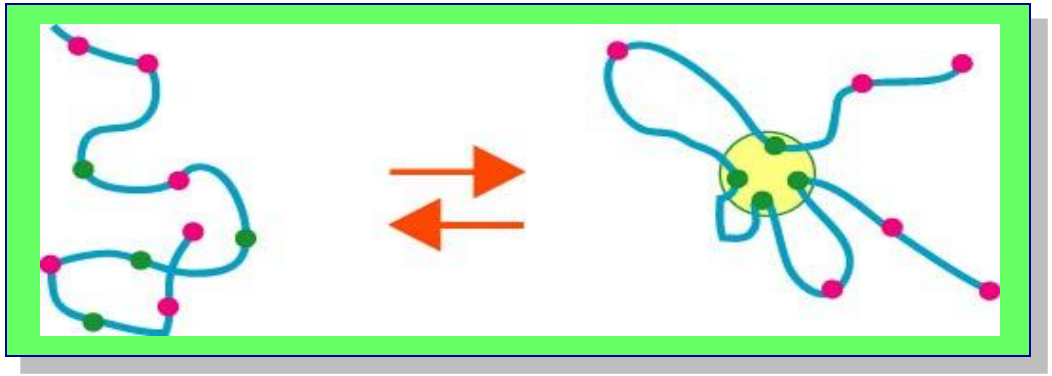
Polymer adsorbtion on a "point"



Equivalent problem: wetting of a disordered substrate:



Some known resultes:



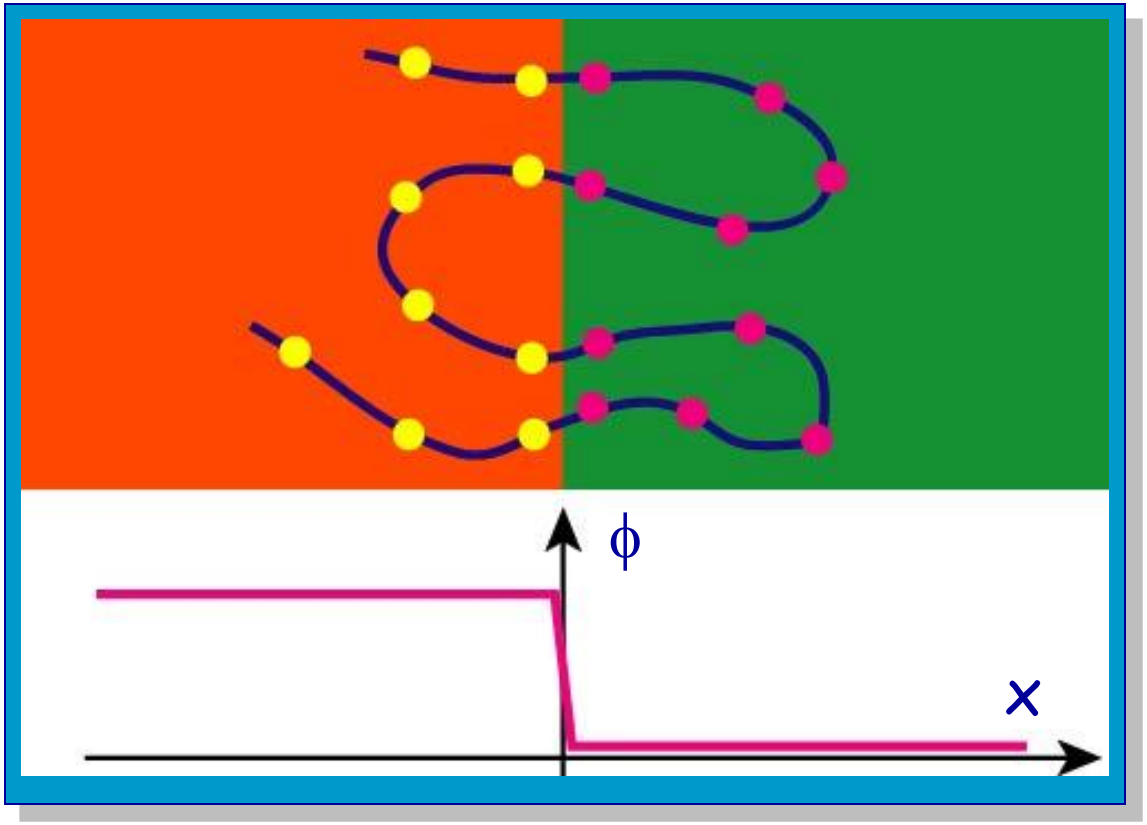
$$e^{-\phi/T}=1+\beta\ \delta(x)$$

- For a **homo**polymer, adsorbtion at $\beta>\beta_c$ where $\beta_c=0$ at $D<2$ and $\beta_c>0$ at $D>2$.
- For a **hetero**polymer, the transition is at $\langle\beta\rangle=\beta c$

A.G., E.Shakhnovich, May 8, 1986;
H.Orland et al, July 11, 1986.

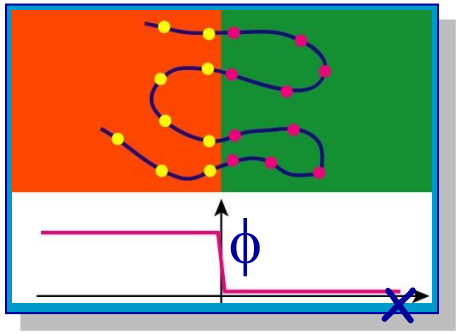
Examples:

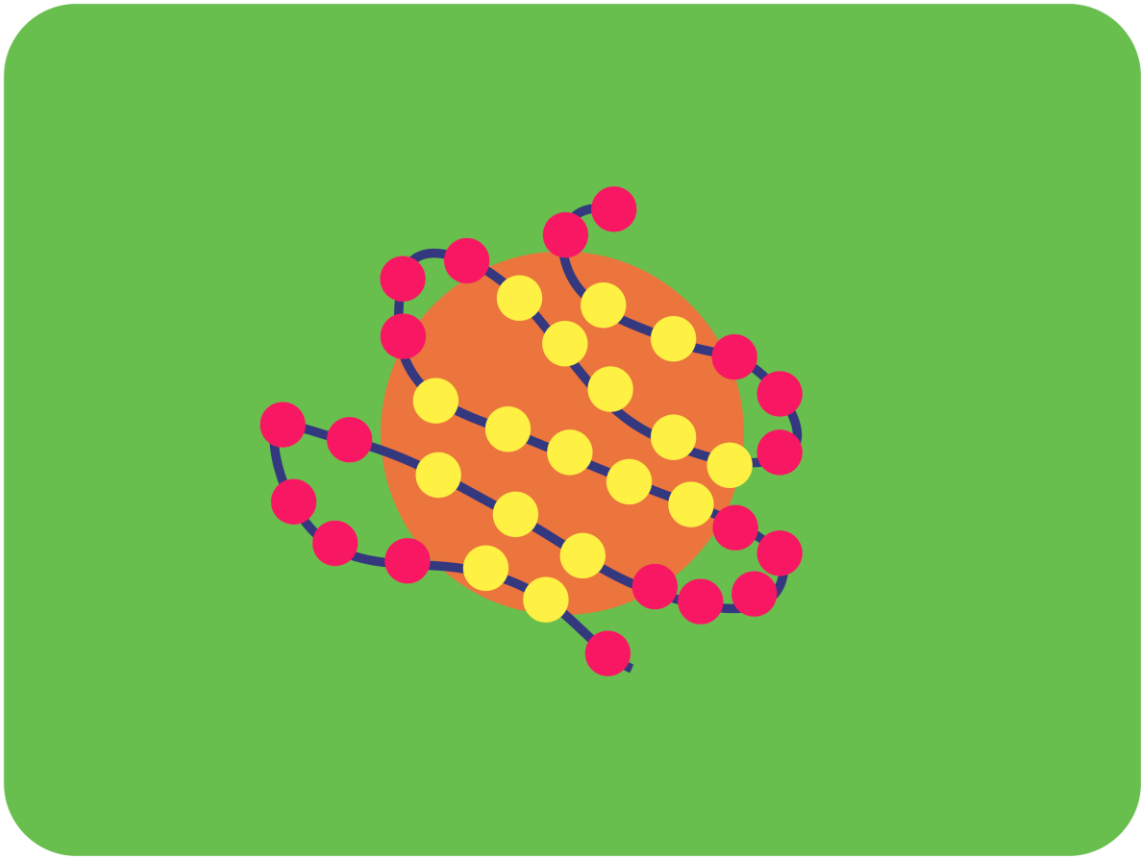
Localization at the interface



No analog for a homopolymer…

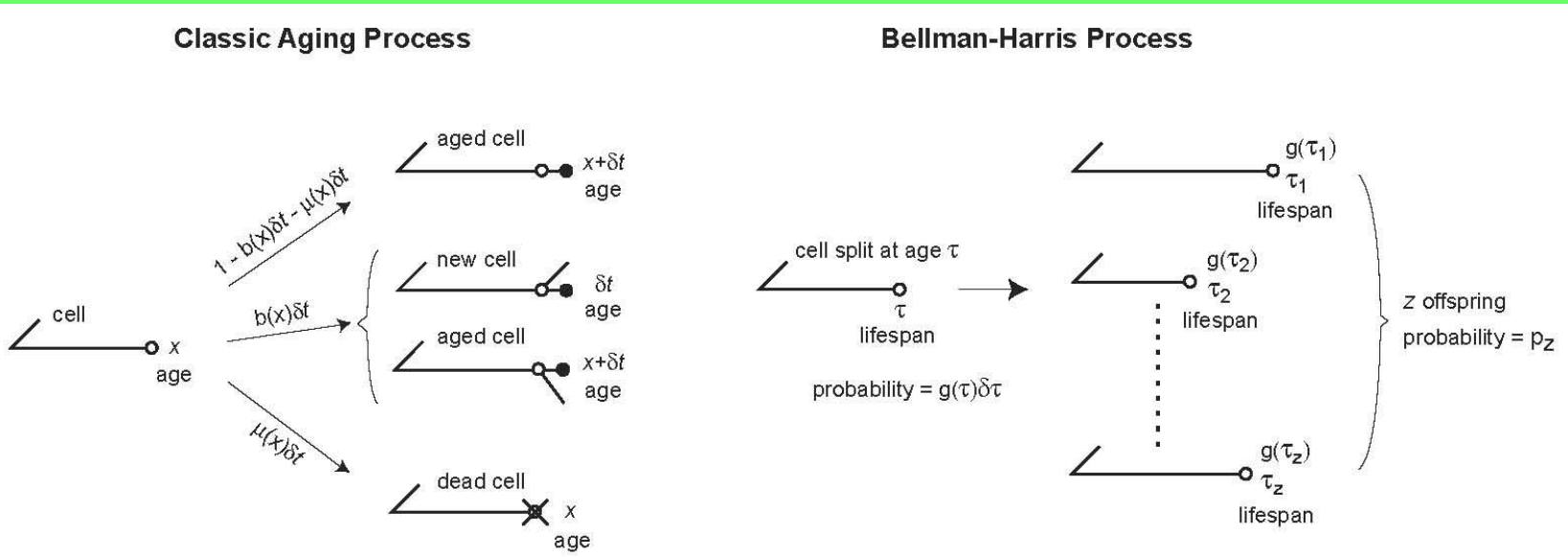
If drawn in a spherical version, then reminds a protein:



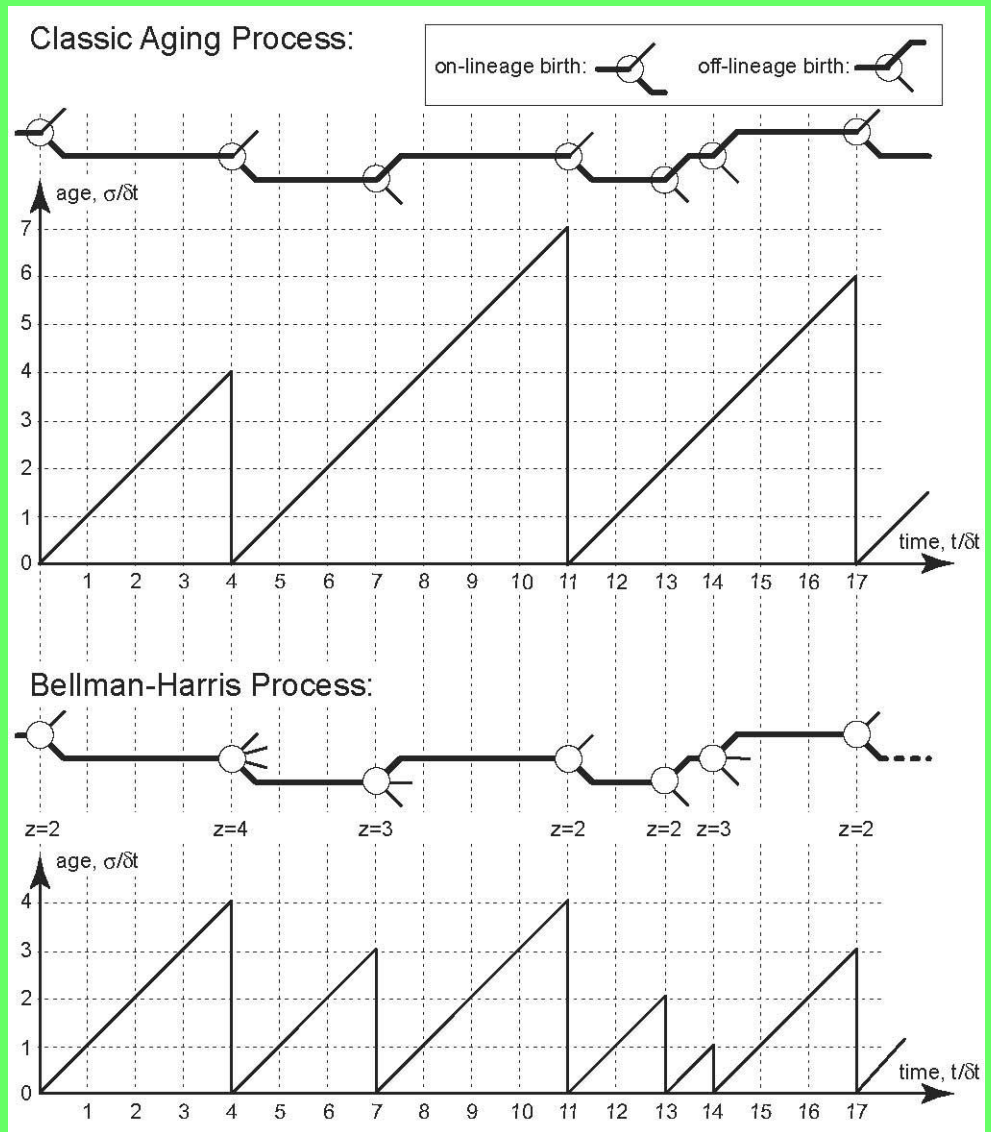


No analog for a homopolymer…

Similar ideas apply to aged structured populations

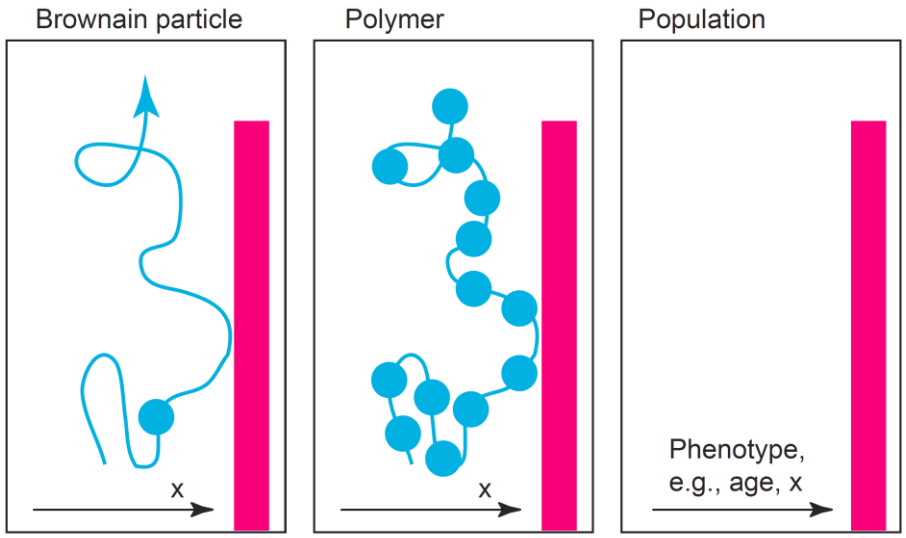


Path in age space



The mathematical machinery of the calculation employs path integrals, most widely known from Feynman formulation of quantum mechanics

Subtleties: boundary conditions

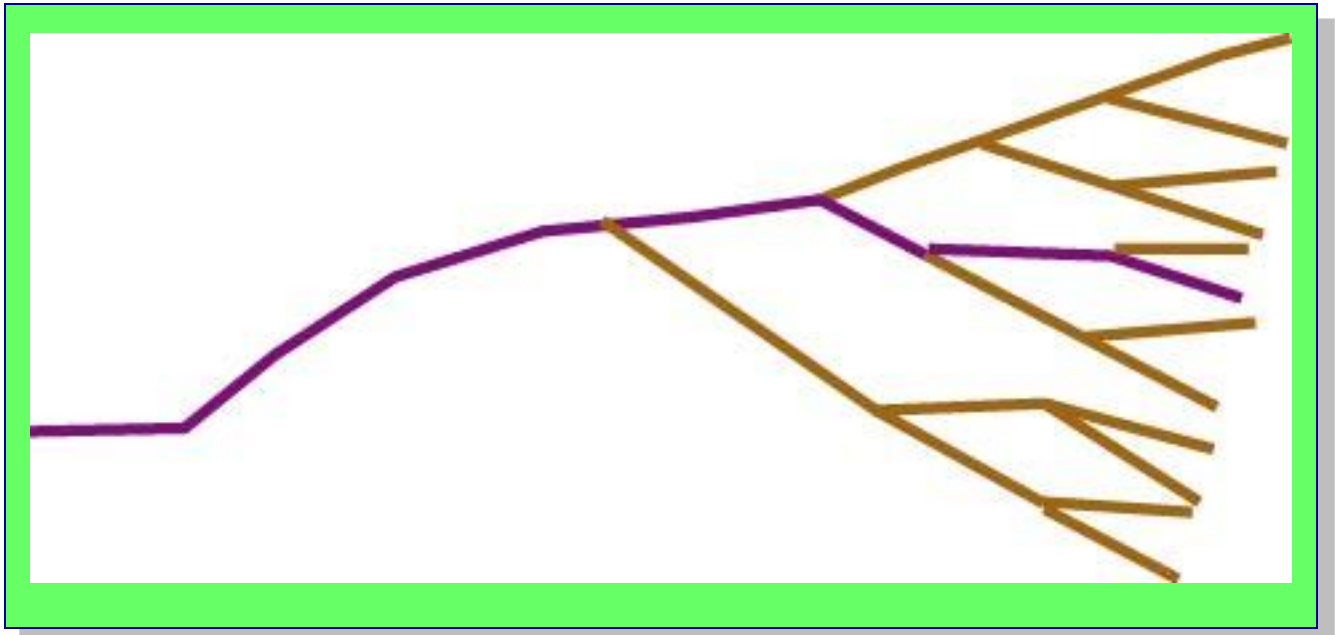


Flux through
the boundary = 0,
dc/dx=0

"Concentration"
at the boundary = 0,
c=0

"Concentration"
at the boundary = 0,
c=0

Conformation: one particular line in the tree



"Energy" is the property of an organism determined by its entire ancestral hystory.

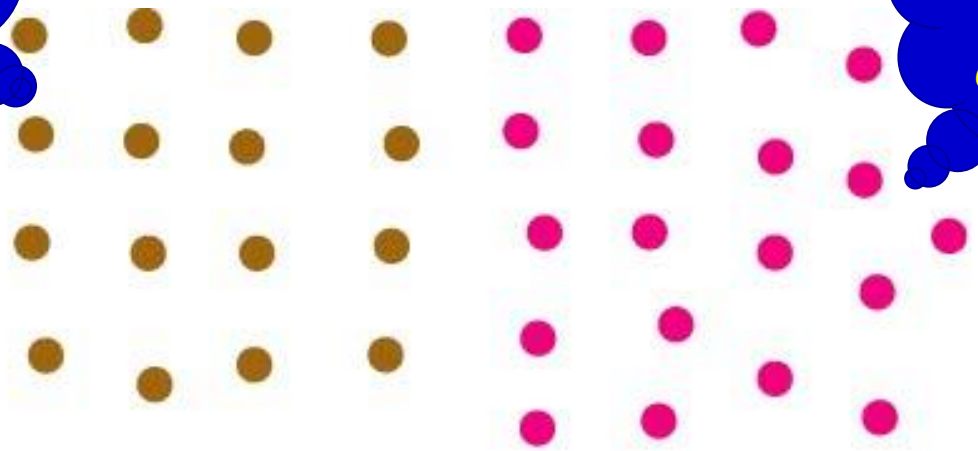
Density distribution etc

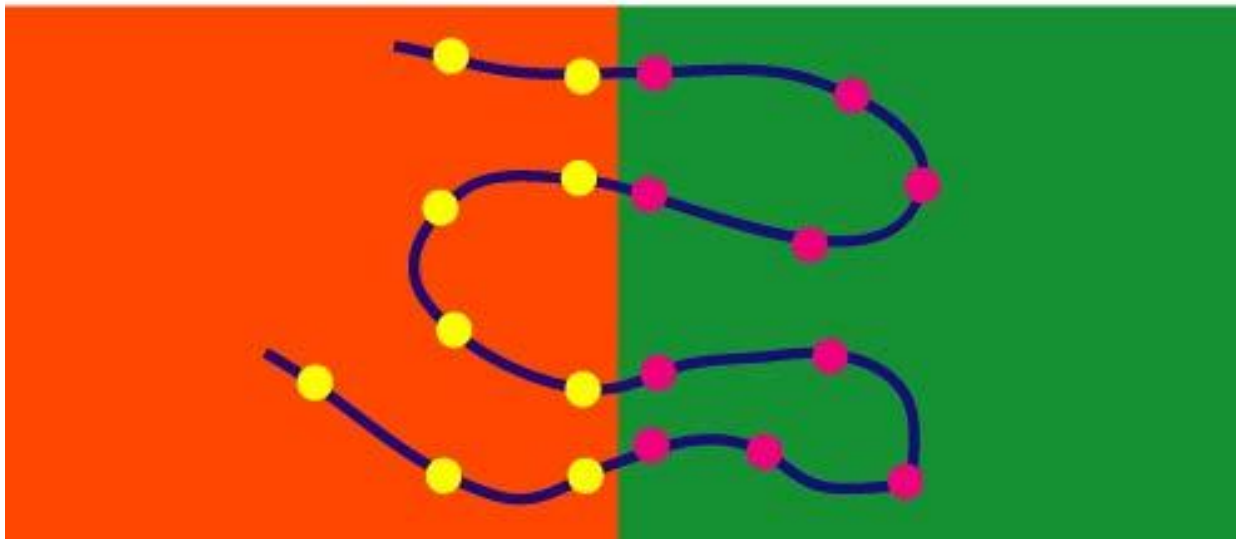
Heteropolymer thermodynamics	Population dynamics
Position along chain t	Time t
Spatial position r	Phenotype i
Monomer sequence $\alpha(t)$	Environment $\mathcal{E}(t)$
External field ϕ_r^α	Reproduction rates $f_i^{\mathcal{E}}$
Green's function $G_r(t)$	Population vector $X_i(t)$
Partition function $Z(t)$	Population size $N(t)$
Free energy $\mathcal{F}$	Lyapunov exponent Λ
Polymer conformation $r(t)$	Organism history $\sigma(t)$
Monomer density n_r^α	Ancestral distribution $\mu_i^{\mathcal{E}}$

Mapping to populations:

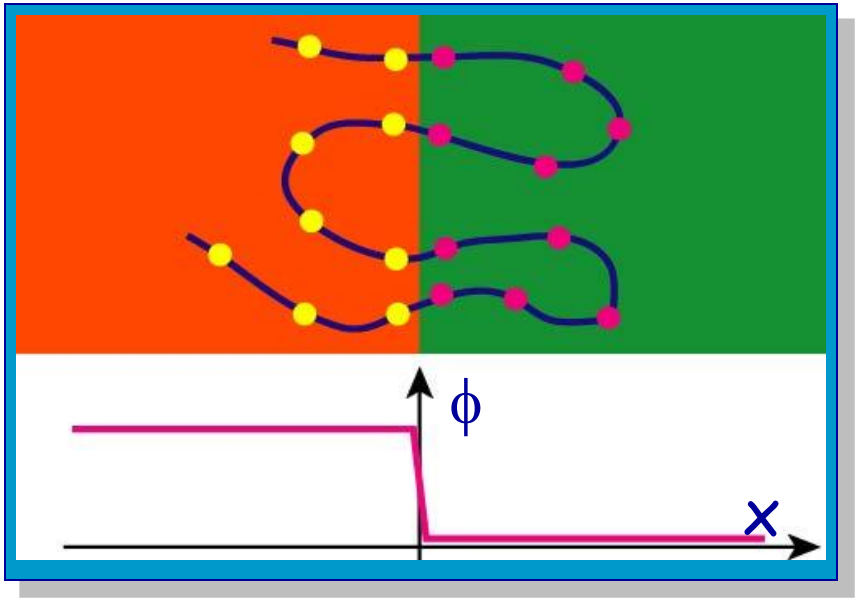
These phenotypes prefer environment O

These phenotypes prefer environment G





Conditions of localization:

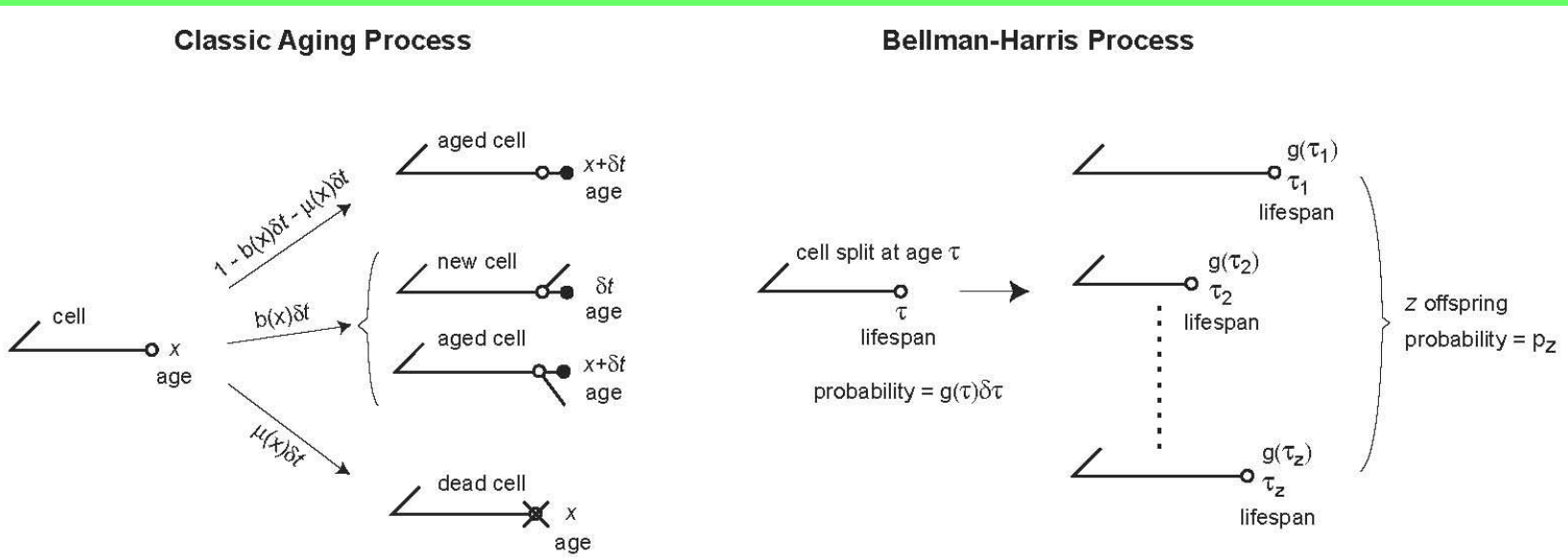


- Energy preference should be sufficient to pay for entropy of localization to half space: $\varepsilon > kT \ln\tau$
- Overall width must be large enough to house a loop: $R > (a\,\tau)^{1/2}$

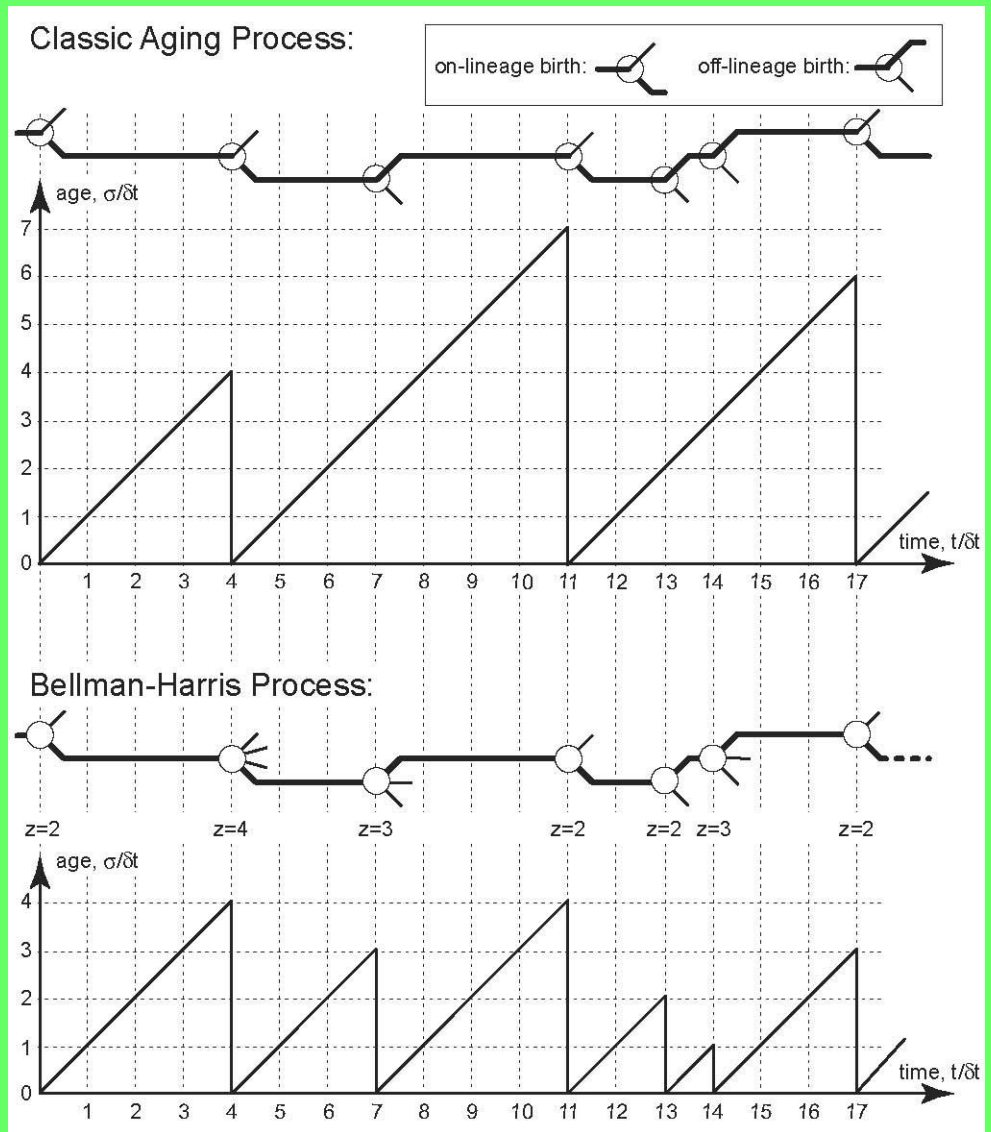
In population language: $M^2/h > \tau > 1/f$

M – total number of phenotypes; f – growth rate; h – switching rate; t – typical time of environmental change.

Detailed formulation of the model



Lineage: path in age space



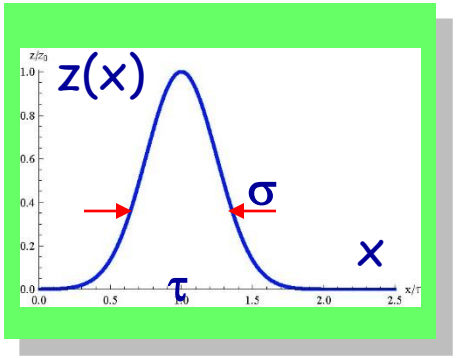
The mathematical machinery of the calculation employs path integrals, most widely known from Feynman formulation of quantum mechanics

Malthus parameter:

- Reproductive function k(x)=b(x)z(x)l(x), where b(x) is the rate of parenting at age x, z(x) is the number of offspring at age x, and l(x) is the probability to live till age x.
- Overall growth rate of population m – solution of Malthus equation:

$$\int_0^\infty k(x)e^{-mx}dx = 1$$

Simple naïve example



- Number of offspring at age x:

$$z(x) = z^* \exp\left[-\frac{(x-\tau)^2}{2\sigma^2}\right]$$

- Organisms never die: l(x)=1;
- Age-independent birth rate, b(x)=b;
- Then solving Malthus equation is easy:

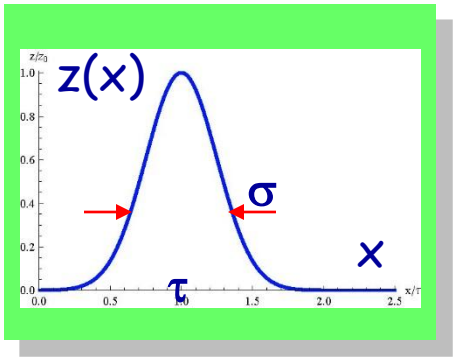
$$m = \frac{\tau}{\sigma^2}\left(1 - \sqrt{1 - \frac{2\sigma^2}{\tau^2}\ln Z_{\text{tot}}}\right)$$

$$Z_{\text{tot}} = \int_0^\infty k(x)dx = b\sigma z^* \sqrt{2\pi}$$

For population to grow (m>0), the number of offspring must be Z_{tot}>1

How does population do it? Idea 1:

One possibility is to "have kids" at the optimal age τ, then population size after time t is:



$$(z^*)^{t/\tau} = e^{t \ln z^*/\tau} \quad \Longrightarrow \quad m_0 = \frac{\ln z^*}{\tau}$$

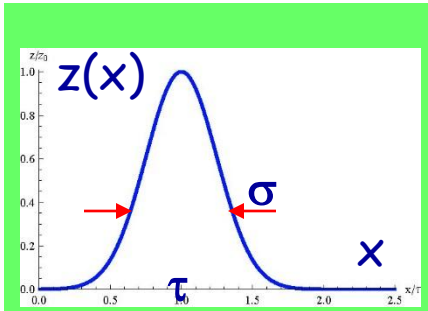
If $b\sigma$ is large, then $m > m_0$, so population does something clever

$$m = \frac{\tau}{\sigma^2}\left(1 - \sqrt{1 - \frac{2\sigma^2}{\tau^2}\ln Z_{\rm tot}}\right)\Bigg|_{\sigma \ll \tau} \simeq \frac{\ln Z_{\rm tot}}{\tau}$$

$$Z_{\rm tot} = \int_0^\infty k(x)dx = b\sigma z^* \sqrt{2\pi}$$

How does population do it? Idea 2:

If we "have kids" a bit before the optimal age τ, then population looses on z(x), but gains on the number of generations over time t: $(z(x))^{t/x}$ has optimum and then



$$m_1 = \frac{\ln z^*}{\tau}\left(1 + \frac{\sigma^2}{\tau^2}\ln z^*\right)$$

If $b\sigma$ is large, then $m > m_1$, so population does something

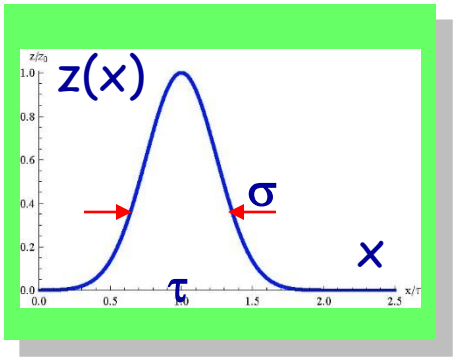
even more clever!!!

$$m = \frac{\tau}{\sigma^2}\left(1 - \sqrt{1 - \frac{2\sigma^2}{\tau^2}\ln Z_{\rm tot}}\right)\Bigg|_{\sigma \ll \tau} \simeq \frac{\ln Z_{\rm tot}}{\tau}$$

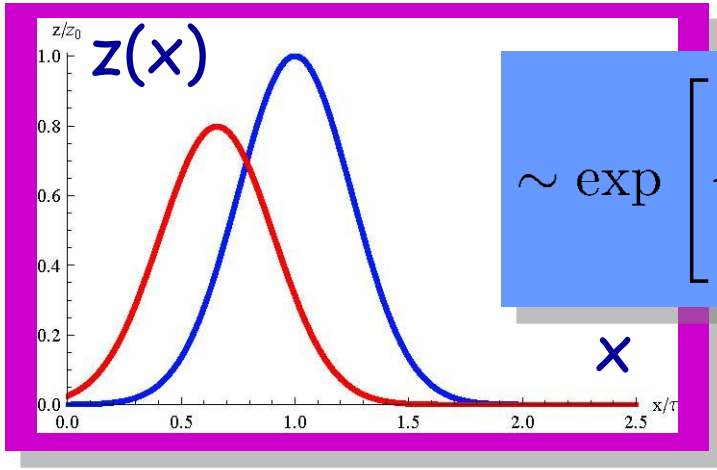
$$Z_{\rm tot} = \int_0^\infty k(x)dx = b\sigma z^*\sqrt{2\pi}$$

How does population do it? Idea 3:

There is a diversity of various strategies, and population uses the fact that there are MANY of them: **entropy of lineages**



Actual distribution of ages at division:



$$\sim \exp\left[-\frac{\left(x-\tau\sqrt{1-\frac{2\sigma^2}{\tau^2}\ln Z_{\rm tot}}\right)^2}{2\sigma^2}\right]$$

$$m = \frac{\tau}{\sigma^2}\left(1-\sqrt{1-\frac{2\sigma^2}{\tau^2}\ln Z_{\rm tot}}\right)\Bigg|_{\sigma\ll\tau} \simeq \frac{\ln Z_{\rm tot}}{\tau}$$

$$Z_{\rm tot} = \int_0^\infty k(x)dx = b\sigma z^*\sqrt{2\pi}$$

Comparison with experiment